DETAILED ACTION

Status of Claims

1. Claims 4, 14, 18, and 24-28 are pending.

Claims 4, 14, and 18 are rejected.

Claims 24-28 are allowed.

Claims 1-3, 6-13, 15-17 and 19-23 are cancelled.

Response to Amendment

Claim Rejections - 35 USC § 112

2. After consideration of Applicants remarks, filed March 9, 2009, the rejection of claims 24-28 under 35 U.S.C. 112, first paragraph is withdrawn.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 4, 14 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These claims are indefinite because the formula in claim 4, filed March 9, 2009, does not contain R10.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 4, 14 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ghai et al. (US 2002/0028852 A1) in view of Seyedi et al. (US 6,743,937 B2) and further in view of Orsini et al. (Carbohydrate Research, Vol. 301, Issue 3-4, June 1997,

pp. 95-109), for the reasons given in the previous office action, mailed November 7, 2008.

Response to Arguments

Rejection of Claims 4, 14 and 18 under 35 U.S.C. 103(a) as being unpatentable over Ghai et al. (US 2002/0028852 A1) in view of Seyedi et al. (US 6,743,937 B2) and further in view of Orsini et al. (Carbohydrate Research, Vol. 301, Issue 3-4, June 1997, pp. 95-109)

9. Applicant's arguments filed March 9, 2009 have been fully considered but they are not persuasive.

The Applicants submit the following: A close reading of the claims 4, 14 and 18 of the present invention shows that the compounds of the present invention differ from those of the art taught by Ghai not just because they are phosphorylated, but because they are a different class of compound: the resverastatin compounds of the present invention are 3,5-dimethoxy-4-hydroxy-stilbene. The teaching of Ghai highlighted by the Examiner on the other hand is of a compound that is a 3,5-4'-trihydroxy-stilbene. Hence there is a fundamental molecular structural difference between the novel compounds of the present invention and the trihydroxy-stilbene taught by Ghai.

This argument is not persuasive. The disclosure highlighted by the Examiner included the entire disclosure, in particular paragraphs 0015, 0016, 0026, 0031 and 0032 (see paragraph 10 of the office action, mailed November 7, 2008). In paragraph 0016 Ghai et al. disclose analogs of resveratrol, which include methoxylated compounds such as 3,5-dimethoxystilbene and 3,4',5-trimethoxystilbene. Thus,

although the compounds of Ghai et al. are not exactly the same as the resverastatin compounds of the present invention, they are close in structural similarity.

The Applicants submit the following: Nothing in the combined disclosure of Ghai, Seyedi and Orsini provides a teaching of all of the elements of the claims compound. The combined art does not teach that the hydroxy groups that are present at each of positions 3 and 5 of 3,5-4'-trihydroxy-stilbene taught by Ghai should be replaced by -OCH3 (methoxy groups) or could be replaced and yet still produce an active compound. In the absence of such teachings, there seems to be little point in proceeding to a discussion of yet another class of compounds: the combretastatin A-4 compound of Seyedi and phosphorylation thereof. Indeed as explained in the current specification, it was an objective of the present invention to provide alternative active derivatives of combretastatin A-4.

This argument is not persuasive. As discussed above, In paragraph 0016 Ghai et al. disclose analogs of resveratrol, which include methoxylated compounds such as 3,5-dimethoxystilbene and 3,4',5-trimethoxystilbene. It is disclosed in paragraph 0026 that analogs of resveratrol have biological activity related to preventing progression of cancer in cells. Thus, not only does Ghai et al. disclose that hydroxy substituents of resveratrol can be replaced with methoxy substituents, but that even with the replacement the compounds are still active against the progression of cancer in cells. With regard to the combretastatin A-4 compound of Seyedi et al., they not only are close in structural similarity to the instant compounds and the compounds of Ghai et al., but they have a similar utility in that they inhibit cancer cell growth (see for example column 1, lines 33-54 of Seyedi et al.

The Applicants submit the following: Moreover, the specific compound of the present invention, 3,5-dimethoxy-4-hydroxy-stilbene (resverastatin) much like resveratrol, is essentially inactive

against the assembly of tubulin as noted in the application (See Tables I-II). In addition, resverastatin also functions as a very useful antifungal and antibacterial substance and that data is also included in the specification (See Tables I-II). Combretastatin A-1 and A-4 do not possess these properties.

This argument is not persuasive. The fact that resverastatin, resveratrol and Combrestatin A-1 and A-4 do not possess every property in common does not negate the fact that they all share at least one common property and that is treating cancer, which is the property that is claimed in instant claim 18.

The Applicants submit the following: None of the stilbenes taught in the combination of references corresponds to the resverastatin claimed in the present invention and there is no teaching in the art that suggests that modification of the stilbenes in the prior art to specifically methylate the 3,5-dihydroxy groups of resveratrol would have produced a substance with biological properties that so closely mimic those of resveratrol.

This argument is not persuasive for reasons given above.

The Applicants submit the following: Much-like the case in Eisai v. Dr. Reddy, while 3,5,4 trihydroxystilbene compounds may well have been known in the art and their modification to phosphorylated groups may well have been suggested, that alone is not sufficient to support prima facie obviousness of a claim to a 3,5-dimethoxy-4-hydroxy-stilbene (resverastatin) that may be phosphorylated. The examiner must show the art teaches the desirability of changing just the 3,5 hydroxy groups to methoxy groups and couple that teaching with a suggestion that making those changes will still produce an active compound. The Examiner simply has not shown why the skilled artisan would have modified a 3,5-4'-trihydroxy-stilbene into a 3,5-dimethoxy-4-hydroxy or that it would be expected to have good activity.

This argument is not persuasive. In paragraph 0012 of Ghai et al. it is disclosed that analogs of the natural product resveratrol with additional hydroxy or methoxy substituents have biological activity that can lead to disease prevention. One of the analogs explicitly disclosed is one having only the 3 and 5 hydroxy substituents replaced with methoxy substituents (see paragraph 0013). Thus, there is a suggestion/motivation by Ghai et al. that replacement of only the hydroxy substituents at positions 3 and 5 of resveratrol with methoxy substituents will still give compounds that have biological activity.

The Applicants submit the following: In regard to the activity of the compounds issue, 3,5-dimethoxy-4-hydroxy stilbene compound of the present invention and its phosphate prodrug represent new compositions of matter that would not have been predicted to have good properties as anticancer agents but not significantly inhibit tubulin. Even in its phosphorylated prodrug form, the 3,5-dimethoxy-4-hydroxy stilbene strongly inhibits growth of the MCF-7 breast cancer cell line (see Tables I and III of the application) and has strong cancer cell growth inhibitory activity among the related benzhydrols and benzophenone new compositions of matter summarized in Table II.

This argument is not persuasive. First, the claims only require treating cancer there no requirement that there be no significant inhibition of tubulin. Second, Seyedi et al. teach that phosphorylation of a compound that is very similar in structure to the claimed compounds as well as the compounds in Ghai et al. did not affect the ability of the compound to act as an anticancer agent (see for example column 2, lines 17-21 of Seyedi et al.).

The Applicants submit the following: Furthermore, Applicants respectfully submit that as a practical matter, the Examiner's statement that "the skilled artisan would have been motivated to phosphorylate the resveratrol analog of Ghai *et al.* as taught by Seyedi *et al.* in order to improve its water solubility is misleading. 3,5-dimethoxy-4-hydroxy stilbene is not taught in the prior art. To arrive at the present invention, the skilled person would not only have to modify the prior art hydroxy compounds they would also have to phosphorylate them and the Examiner has provided no reasoning why a chemist instead of following the ordinary course of preparing an alkali metal salt of the one 3,5-4'-trihydroxy-stilbene would instead both modify the hydroxyl groups of the prior art stilbenes to methoxy groups and then on top of that synthesize a phosphate derivative thereof and then convert the phosphate derivative to an alkali metal phosphate salt and still expect the end compound to be active.

This argument is not persuasive. Although Ghai et al. do not expressly teach the compound 3,5-dimethoxy-4-hydroxy stilbene, this compound is suggested by Ghai et al., since Ghai et al. is directed to methoxylated resveratrols which includes structurally similar compounds such 3,5-dimethoxystilibene. With regard to the suggestion to phosphorylate the resveratrol this is provided by Seyedi et al., which phosphorylates a structurally similar compound which has a similar utility and the phosphorylated compound not only maintains its ability to be effective for use in the treatment of cancer tumors but it has the added advantage of increased water solubility. Based upon the teachings of Seyedi et al. the skilled artisan would have a reasonable expectation of success when phosphorylating the compounds of Ghai et al., since the compounds of Ghai et al. are structurally similar and have similar utility to the compounds of Seyedi et al.

The Applicants submit the following: Moreover, if the skilled person were to proceed as suggested by the examiner to attempt to simply phosphorylate the trihydroxy stilbene of Ghai, *at al.,* the result would have be an extended series of synthetic challenges to prepare a monophosphate of that triphenol or completely phosphorylate to a triphosphate. Both approaches would have been fraught with technical problems and there is no teaching in the cited art as to how to overcome those problems.

This argument is not persuasive because whether or not the phosphorylation is challenging is not determinative of unobviousness. As discussed above Ghai et al. not only disclose trihydroxy stilbene compound but is also directed to methoxylated resveratrols which includes structurally similar compounds such 3,5-dimethoxystilibene. Seyedi et al., phosphorylates a structurally similar compound to those of the instant invention and Ghai et al. which also has a similar utility and the phosphorylated compound of Seyedi et al. not only maintains its ability to be effective for use in the treatment of cancer tumors but it has the added advantage of increased water solubility. Thus, based upon the teachings of Seyedi et al. the skilled artisan would have a reasonable expectation of success when phosphorylating the compounds of Ghai et al., since the compounds of Ghai et al. are structurally similar and have similar utility to the compounds of Seyedi et al.

Rejection of Claims 24-28 under 35 U.S.C. 103(a) as being unpatentable over Orsini et al. (Carbohydrate Research, Vol. 301, Issue 3-4, June 1997, pp. 95-109)

10. Applicant's arguments, see page 18 beginning at paragraph 2 through to page 19, paragraph 1, filed March 19, 2009, with respect to the rejection of Claims 24-28 under 35 U.S.C. 103(a) as being unpatentable over Orsini et al. (Carbohydrate

Research, Vol. 301, Issue 3-4, June 1997, pp. 95-109) have been fully considered and are persuasive. The rejection of claims 24-28 has been withdrawn.

Allowable Subject Matter

11. Claims 24-28 are allowed.

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosalynd Keys whose telephone number is (571)272-

0639. The examiner can normally be reached on M & T 5:30 am-7 am & 9:30 am-4:30 pm: W-F 8:00 am-4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel Sullivan can be reached on 571-272-0779. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Rosalynd Keys/
Primary Examiner, Art Unit 1621

June 12, 2009